Management of pneumonia in critically ill patients

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Series explanation: State of the Art Reviews are commissioned on the basis of their relevance to academics and specialists in the US and internationally. For this reason they are written predominantly by US authors

ABSTRACT

Severe pneumonia is associated with high mortality (short and long term), as well as pulmonary and extrapulmonary complications. Appropriate diagnosis and early initiation of adequate antimicrobial treatment for severe pneumonia are crucial in improving survival among critically ill patients. Identifying the underlying causative pathogen is also critical for antimicrobial stewardship. However, establishing an etiological diagnosis is challenging in most patients, especially in those with chronic underlying disease; those who received previous antibiotic treatment; and those treated with mechanical ventilation. Furthermore, as antimicrobial therapy must be empiric, national and international guidelines recommend initial antimicrobial treatment according to the location's epidemiology; for patients admitted to the intensive care unit, specific recommendations on disease management are available. Adherence to pneumonia guidelines is associated with better outcomes in severe pneumonia. Yet, the continuing and necessary research on severe pneumonia is expansive, inviting different perspectives on host immunological responses, assessment of illness severity, microbial causes, risk factors for multidrug resistant pathogens, diagnostic tests, and therapeutic options.

Introduction

Pneumonia is a major health problem, being associated with high morbidity and short and long term mortality. It is also the leading infectious disease cause of mortality among all ages worldwide.[1 2] Pneumonia in critically ill patients may present as pneumonia acquired in the community (community acquired pneumonia, CAP); pneumonia acquired in the hospital (hospital acquired pneumonia, HAP); or pneumonia related to mechanical ventilation (ventilator associated pneumonia, VAP). Severe pneumonia is associated with high short and long term mortality, and those who survive often have important sequelae such as alterations of lung function, reduction in mental and cognitive functions, weakness and reduction of motor function, and reduced functional autonomy.[3 4] Appropriate diagnosis of severe pneumonia is crucial to improve survival of critically ill patients. Identifying a pathogen is critical for antimicrobial stewardship in critically ill patients with severe pneumonia. However, in most patients, identifying the cause is challenging, especially in those with chronic underlying disease, those who received previous antibiotic therapy, and those treated with mechanical ventilation. Prompt and adequate antimicrobial treatment is crucial for the best outcomes in critically ill patients with severe pneumonia, and is a key focus of international guidelines for the management of pneumonia.[5-7]

In this article, we review current knowledge on the management of pneumonia in critically ill patients, including CAP and HAP, focusing on epidemiology, microbial etiology, pathogenesis, treatment, and prevention.

Sources and selection criteria

We searched databases from 2000 to 2021, including PubMed, Medline, the Cochrane Database of Systematic Reviews, and the Central Register of Controlled Trials (clinicaltrials.gov). We used both keywords and keyword combinations, including "pneumonia", "severe respiratory infection", "severe pneumonia", "pneumonia in critically ill", "community acquired pneumonia", "intensive care pneumonia", "hospital acquired pneumonia", "ventilator associated pneumonia", "management of pneumonia", "diagnosis of pneumonia", and "pneumonia therapy". We reviewed relevant titles and abstracts of this search and prioritized studies in English, considering meta-analyses, systematic reviews, international guidelines, randomized controlled trials (RCTs), and large, descriptive and observational studies. We include some additional, relevant articles published before 2000.

Defining severe pneumonia and its epidemiology

Severe community acquired pneumonia (SCAP)

Early identification of patients with SCAP is critical to provide rapid, definitive treatment and to avoid delay

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in providing intensive care treatment, in an effort to reduce mortality.[8 9] Multiple scoring systems provide support in deciding the site of care, but most of these tools predict mortality risk, and not specifically the need for intensive care admission. Proper site of initial care is important, since both length of hospital stay and mortality of patients first admitted to the general ward and then transferred to the intensive care unit (ICU) are higher than for patients directly admitted to the ICU.[10 11]

The most widely accepted criteria for defining severe CAP are from the 2007 Infectious Disease Society of America/American Thoracic Society (ATS/IDSA) consensus guidelines on the management of CAP in adults[12] (box 1). ICU care is needed for those who require mechanical ventilation or vasopressor support of shock, or the presence of three of nine minor criteria. Several validation studies[13-17] of the minor criteria found that they were accurate for predicting need for ICU admission.

The number of patients requiring intensive care is growing, along with the rising number of individuals who are older, immunocompromised, or with underlying serious comorbidities. In 2018, a cross sectional study[18] showed a substantial increase in hospitalization for acute respiratory infections throughout the period 2003-15. The rise was more evident in the older population: ICU admission was reported to be 3.3 times higher in patients aged 85-89 and 5.8 times higher in patients ≥90, compared with younger populations.

A secondary analysis of a prospective, population based cohort study on hospitalized patients with CAP in the US found that 23% needed ICU admission, of whom 24% required invasive mechanical ventilation and 20% required non-invasive mechanical ventilation. The authors reported an incidence of CAP in the ICU of 145 cases per 100 000 adults per year.[19]

CAP is also a major cause of sepsis. In 2016, the third international consensus definition (Sepsis-3) defined sepsis as an increase in the Sequential Organ Failure Assessment (SOFA) score of two points or more, and recommended the use of the quick Sequential Organ Failure Assessment (qSOFA) score to identify patients at high risk of death and prolonged ICU stay among those with suspected infection, such as CAP.[20] Several studies evaluated the performance of qSOFA in a CAP population,[21-27] and showed that it was more accurate than other scores, such as CRB (confusion, respiratory rate, blood pressure), and SOFA in predicting mortality and ICU admission. In spite of early recognition and treatment of SCAP, short and long term mortality remain high (27-50%).[19]

Box 1: ATS/IDSA criteria for severe CAP

Minor criteria

- Respiratory rate ≥30 breaths/min
- PaO_2/FiO_2 ratio ≤250
- Multilobar infiltrates
- Confusion/disorientation
- Uremia (blood urea nitrogen level ≥20 mg/dL)
- Leukopenia (white blood cell count <4 ×10^9/L)
- Thrombocytopenia (platelet count <100 ×10^9/L)
- Hypothermia (core temperature <36°C)
- Hypotension requiring aggressive fluid resuscitation

Major criteria

- Invasive mechanical ventilation
- Septic shock with the need for vasopressors

Hospital acquired pneumonia (HAP)

HAP has an estimated annual incidence of five to 10 cases per 1000 hospital admissions globally, and is considered the second most common hospital acquired infection.[7] One subgroup, ventilator associated pneumonia (VAP), which occurs in patients on mechanical ventilation for at least 48 hours, affects 10-25% of all ventilated patients, with the risk being highest in the first 5-7 days of mechanical ventilation.[5 7] VAP remains a frequent nosocomial infection in the ICU, and causes significant morbidity. However, debate continues on attributable mortality rates, varying widely and being affected by diverse confounders.[28 29] With the implementation of recent, effective prevention strategies, however, incidence and mortality have been decreasing.[30-33] In addition to VAP, some patients with severe HAP deteriorate and then require mechanical ventilation for management, and this population is referred to as ventilated HAP (fig 1).

HAP develops after ≥48 hours of hospitalization and is classified as HAP in the ward, with a mortality rate of 13-28%. HAP in the ICU (non-ventilated ICU HAP) has a mortality of 15%, and VAP and ventilated HAP have a mortality rate of up to 28%.

In epidemiological studies, the average rate of VAP in the US is four cases per 1000 days of mechanical ventilation,[5 34] which represents half the rate reported in Europe: 9.5 cases per 1000 days of mechanical ventilation.[35] In recent years, the incidence of VAP has gradually declined in the US and in Europe, possibly in relation to the implementation of preventive care bundles.[36 37] However, the use of surveillance definitions developed by the Centers for Disease Control and Prevention (CDC) resulted in concern about the accuracy of the VAP definition, especially as rates dropped but mortality did not. These VAP definitions have recently been supplemented by ventilator associated event (VAE) reporting. The updated definitions include any condition that is associated with a decline in oxygenation. Incidence of VAP is greater than with the previous definition, although VAE may not always be the result of infection, and is of unclear significance as a measure of ICU quality of care. Furthermore, it is not widely used in Europe.[38]

In the US, some quality initiatives have a goal of "zero ventilator associated pneumonia" (ZERO-VAP)[38]; however, concerns about the ZERO-VAP target have been raised.[39] First, it is difficult to quantify and determine the eradication of a preventable disease

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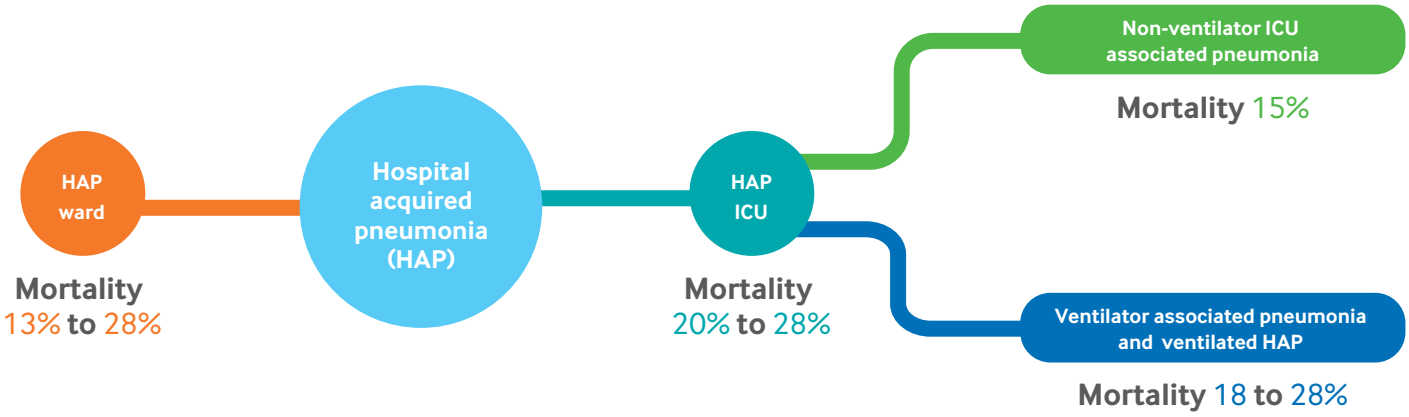

Fig 1 | Spectrum of hospital acquired pneumonia

without accurate and reliable diagnostic methods, and no gold standard exists for diagnosing VAP. Second, the CDC VAP definition can be manipulated, leading to an underestimation of occurrence of VAP. Third, monitoring adherence to long term prevention measures poses a notable challenge. To determine the efficacy of interventions in reducing VAP, innovative diagnostic markers and the application of improved research methods are needed.

HAP and VAP are considered leading causes of death from nosocomial infection.[4 28 40 41] Mortality in the US is approximately 13%,[5] but a recent prospective and multicenter observational study[42] indicated that 30 day mortality caused by VAP was 30% in Europe. Similarly, after analyzing data of 14 212 patients admitted to the ICU for more than 48 hours, a separate French observational study reported that the risk of 30 day mortality increased by 82% in patients with HAP and 38% in patients with VAP.[43] Compounding these findings is an analysis of non-inferiority endpoints by Talbot et al[44] that examined seven bacterial HAP/VAP datasets and reported that 28 day all-cause mortality was higher in ventilated HAP (28%), followed by VAP (18%) and non-ventilated HAP (15%). These results highlight the influence of patient related factors on outcomes, as reported in a previous, prospective observational study,[45] and underpin the impact of preventive measures.

Antibiotic resistance is a major concern in HAP/VAP globally, especially because of its association with prolonged length of hospital stay and higher mortality. Gram negative microorganisms are the pathogens that most frequently cause HAP/VAP.[46] In an observational, 24 hour point prevalence study[46] of 15 202 ICU patients from 1155 centers across 88 countries, infections caused by *Enterococcus* resistant to vancomycin, *Klebsiella* resistant to α-lactam antibiotics—including third generation cephalosporins and carbapenems, or *Acinetobacter* species resistant to carbapenem—were independently associated with a higher risk of death. These findings emphasize the importance of knowing local epidemiology and risk factors for multidrug resistant pathogens to target the most likely etiologic pathogens in patients with HAP/VAP.

New concepts in pneumonia pathogenesis

CAP and cardiovascular disease

In addition to its short term sequelae, CAP has long term implications for mortality that may be related to heart disease as a complication of pneumonia.[47] Approximately 8-25% of patients with CAP have been reported to experience at least one cardiac event during hospitalization,[48-50] including acute coronary syndrome, new or worsening heart failure, new or worsening arrhythmias, and acute stroke.[51 52] Such events are more commonly reported in patients with chronic cardiovascular disease, in severe cases of pneumonia, and in conditions related to pathogens, such as pneumococcus and influenza virus,[53-55] but they can also occur in patients without chronic cardiovascular disease.[56]

The pathogenesis of cardiac dysfunction in pneumonia is multifactorial, involving host factors, pathogens, and medication.[51 57 58] A great proportion of hospitalized CAP patients are older adults with comorbidities (chronic pulmonary disease, chronic cardiovascular disease, diabetes mellitus), who may have chronic endothelial dysfunction.[59-61] During the acute phase of pneumonia, inflammation occurs in the lungs, but a systemic inflammatory response also occurs that augments the release of pro-inflammatory cytokines, which could directly or indirectly injure the myocardium.[62]

Streptococcus pneumoniae (pneumococcus) is the most common bacterial pathogen in CAP, and clinical and animal data have shown that the organism can invade the myocardium directly and cause cardiac damage.[63] Pneumolysin, the most important virulence factor of pneumococcus, can also cause cardiomyocyte necroptosis[64] (a programmed mode of cell death that increases inflammation), which may result in cardiac damage.[65] Similarly, pneumococcal bacteremia is known to be a risk factor for cardiac events,[66] with the risk lasting for up to 10 years after the pneumonia episode.[62 66] Shenoy et al,[67] in an experimental study of pneumococcus, reported that cardiac damage

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depends on the ability of a clinical isolate to cause high grade bacteremia, and pathological damage may depend on the pneumococcal strain. Respiratory viruses, identified using new molecular testing, are frequently reported as a cause of CAP, and they too can cause cardiac injury. A self-controlled case series reported an increase in the risk of myocardial infarction during the week after laboratory confirmed infection with influenza virus. This risk was six times higher when compared with the risk present during the year before or after infection. Importantly, an elevated incidence of acute myocardial infarction after influenza infection was observed in adults aged ≥65.[68] Compounding these findings is a time series analysis of English hospital admissions, in which a small yet strongly significant correlation was noted between weekly occurrence of new acute myocardial infarction or ischemic stroke hospitalization in older adults, especially in patients aged ≥65 with positive laboratory results for respiratory viruses (including influenza, para-influenza, respiratory syncytial virus, human metapneumovirus, rhinovirus, and adenovirus).[69] Replication of respiratory viruses within the myocardium may lead to a cascade of inflammatory processes that causes fibrosis and, thereby, cardiac necrosis. It may also lead to alterations in lipid metabolism, by which the course of atherosclerosis would be accelerated, and serve as a possible mechanism for cardiac damage.[70 71] Several mechanisms have been suggested to help explain cardiac effects as sequelae of viral infection; however, we do not yet have complete understanding of the exact mechanisms, or the ideal approach to prevention.

VAP and the endotracheal tube

Endotracheal intubation allows pathogens to enter directly into the lower respiratory tract, interfering with normal lung defense mechanisms, with the endotracheal tube (ETT) becoming a reservoir for pathogenic microorganisms.[72] Biofilm formation on the tube has two important implications: (1) it causes intra-luminal narrowing that may impede weaning from the ventilator, and (2) bacterial pathogens grow embedded and protected in an extracellular polymeric substance or matrix that makes them more resistant to antimicrobials,[73] and they serve as a nidus of endobronchial infection[74] that is difficult to eliminate.[75] Biofilm is detectable in approximately 95% of endotracheal tubes in ventilated patients, occurring within hours of endotracheal intubation.[76] The most frequent biofilm pathogens are *Acinetobacter baumannii*, *Pseudomonas aeruginosa*, *Staphylococcusaureus*, and *Klebsiella pneumoniae*, and colonization may be the first step toward VAP.[77 78] An observational study[79] reported that biofilm formation, after at least 24 hours, was less in both silicone coated polyvinyl chloride (PVC) and noble metal coated PVC ETTs than in uncoated PVC ETTs.

The role of the microbiome in pneumonia pathogenesis

Multiple bacterial species are present in the healthy lung, which is not, as previously thought, sterile, and they comprise the "lung microbiome."[80] *Prevotella*, *Veillonella*, *Streptococcus*, *Fusobacterium*, and *Hemophilus* species are the most frequently reported bacterial pathogens in this microbiome, which is a dynamic community, with a constant equilibrium among species and in an interaction with lung immunity. In the healthy state, the microbiome comprises a diverse population of organisms, and they are present in a relatively low microbial load.

Acute infection and chronic pulmonary diseases, such as pneumonia, non-cystic fibrosis bronchiectasis,[81] chronic pulmonary obstructive disease (COPD),[82] or asthma[83] disturb the equilibrium of the healthy lung microbiome. This dysbiosis results in changes in microbial communities, often leading to less diversity and an increase in the microbial load.[84] The risk factors for dysbiosis that lead to bacteria such as pneumococcus to cause disease are only partially understood.[85]

In a longitudinal analysis of the lung microbiome in critically ill intubated patients, the authors observed that the biomass of the lung microbiome increased over time.[86] A progressive change also took place in community diversity, as bacterial taxa in the healthy lung are replaced with a less diverse group of organisms, including *Staphylococcus* spp, and *Acinetobacter* spp in patients with pneumonia.[87] In addition, a relation exists between the lung microbiome and lung immunity,[88 89] which shows that the enrichment of the lung microbiome with oral taxa was associated with inflammation in the lung (increased alveolar concentration of inflammatory cytokines, increased alveolar lymphocytes) and a distinct metabolomic profile.

Recently, it was proposed[88] that HAP is not only an acute condition caused by contamination of the lung by exogenous microorganisms, but also the result of a dysbiosis between the lung microbiome and mucosal immunity. This approach could lead to the implementation of new preventive methods to restore immune function, and novel therapies that allow for the manipulation of the lung microbiome instead of its elimination by antibiotics.

Diagnosis of pneumonia

Suspicion and clinical diagnosis of pneumonia in patients coming from the community rely on the presence of acute symptoms (≤7 days) of a lower respiratory tract infection that include cough, expectoration, fever, chills, and dyspnea, together with the presence of a new infiltrate on chest radiograph.[90] Typically, pneumonia symptoms may be less evident in older people, in whom the absence of fever was reported in approximately 30% of patients.[91] Similarly, individuals treated with antibiotics, steroids, and non-steroidal anti-inflammatory drugs may also present with less evident symptoms of lung infection.[92] Other conditions, such as pulmonary embolism, pulmonary edema, and lung cancer, may mimic pneumonia and present with fever and pulmonary infiltrates.[93] It is helpful and important to review prior chest radiographs, if

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possible, to rule out other diseases. Rarely, after a negative chest radiograph, patients may receive a diagnosis of pneumonia by more sensitive methods such as a chest computed tomography (CT) scan.

VAP is usually suspected when patients have symptoms of fever or hypothermia, leukocytosis or leukopenia, and evidence of purulent secretions in an ETT or tracheostomy aspirate, in the setting of a new or progressive lung infiltrate. Data on clinical, radiological, and laboratory parameters often provide the basis for clinicians to initiate antimicrobial treatment in patients with VAP. Interestingly, a systematic review and meta-analysis (including 25 studies and data of 1639 patients)[94] that investigated performance of several diagnostic tests for VAP reported that sensitivity and specificity of physical examination findings for VAP were poor: fever (66.4% [95% confidence interval (CI) 40.7 to 85.0], 53.9% [95% CI 34.5 to 72.2]) and purulent secretions (77.0% [95% CI 64 to 85.9], 39.0% [95% CI 25.8 to 54.0]). The presence of infiltrates on chest radiographs had a sensitivity of 88.9% (95% CI 73.9 to 95.8%) and specificity of 26.1% (95% CI 15.1 to 41.4%); the endotracheal aspirate had a sensitivity of 75.7% (95% CI 51.5 to 90.1) and specificity of 67.9% (95% CI 40.5 to 86.8); and the clinical pulmonary infection score (CPIS) >6 had a sensitivity of 73.8% (95% CI 50.6 to 88.5) and specificity of 66.4% (95% CI 43.9 to 83.3). The study found poor specificity for the classic clinical indicators for VAP diagnosis, highlighting the need for a new diagnostic tool for this condition.

For pneumonia diagnosis, radiographic confirmation is essential. It provides important information on the site, extent, and associated features of pneumonia. The presence of pleural effusion or multilobar involvement serves as an indicator of severity.[6] Reported sensitivity and specificity of chest radiographs in CAP were 66% and 77%, respectively.[95] A standard chest radiograph for CAP consists of posteroanterior and lateral views. However, diagnostic performance of chest radiographs increases with the use of lateral projection images. Chest radiographs have some limitations, as shown by results obtained in a prospective and multicenter interventional study[96] that included 319 patients diagnosed with CAP who had a chest radiograph and thoracic CT scan at admission. In this study, no evidence of pneumonia was present on CT scans in 30% of patients diagnosed with CAP based on the clinical presentation and chest radiograph. Conversely, the CT scan identified up to 35% of pneumonia cases, which had not initially been caught by chest radiographs. These results underpin the potential importance of CT scans as a complementary tool to chest radiographs in diagnosing pneumonia. Further, CT scans could prove helpful in cases with non-specific radiographic findings; pulmonary complications such as empyema or cavitation; clinical suspicion of an underlying lesion such as lung carcinoma; and recurrent or non-resolving pneumonia.[97]

In VAP, clinicians often use chest radiographs to determine evidence of new infiltrates. Radiography is reported as the most widely employed imaging technique in diagnosing this condition.[98] However, chest radiographs are not sensitive or specific for VAP diagnosis.[99 100] Interestingly, lung ultrasound is a promising, non-invasive imaging tool for such diagnoses. A systematic review and meta-analysis[101] that included 12 studies with data of 1515 patients found that lung ultrasounds have a sensitivity and specificity of 88% and 89%, respectively, with an area under the curve (AUC) of 0.95. A separate systematic review and meta-analysis[102] showed that the emergence of sub-pleural consolidations on lung ultrasound in anterior lung regions had a specificity of 95% (95% CI 79% to 99%) on the eve of the day when clinical suspicion was present. On the day when clinical suspicion was present, the emergence of lobar/sub-lobar consolidations in anterior lung regions had a specificity of 100% (95% CI 87% to 100%) while the emergence of lobar/sub-lobar consolidations with dynamic air bronchograms had a specificity of 96% (95% CI 81% to 99%). These data suggest that lung ultrasounds are highly accurate in diagnosing VAP. However, applying this technique requires considerable expertise and practice, especially in mechanically ventilated patients.

Guideline recommendations[6] for microbiological diagnosis in patients with severe CAP include obtaining good quality sputum, blood, and pharyngeal swab samples to detect respiratory viruses in patients with severe illness. Molecular detection through polymerase chain reaction (PCR) is the gold standard for virus diagnosis.[103] Detecting viruses through antigen based assays is limited owing to low sensitivity (40-70%); in cases of negative results, although specificity ranges between 90% and 95%, testing cannot rule out a viral infection diagnosis.[103] Sputum is recommended to be collected before starting antibiotic treatment. Sensitivity for Gram staining of a sputum sample is approximately 80% in cases of pneumococcal pneumonia and 78% in pneumonia caused by *Staphylococcus*; specificity is 93-96%.[104 105] Results of respiratory samples must be interpreted with caution: the detected microorganism may form part of the normal flora or may be present as a result of colonization in the patient.[103] Also, urinary antigen detection testing of *S pneumoniae* and *L pneumophila* has good sensitivity and specificity, and should be performed in those with severe CAP. Finally, bronchoscopic samples such as bronchoalveolar lavage in intubated patients are easy to retrieve and provide information about organisms in the lower respiratory tract.

Debate continues about the best respiratory sampling method and the most accurate diagnostic approach for nosocomial pneumonia. The latest US guidelines[5] recommend non-invasive sampling (endotracheal aspiration) with semiquantitative cultures to diagnose VAP and non-VAP. However, with the aim of reducing antibiotic exposure, the latest European guidelines[7] recommend obtaining distal

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quantitative cultures before antibiotic treatment in clinically stable patients with suspected VAP. Similarly, guidelines also recommend obtaining a sample from the lower respiratory tract (eg, distal or proximal quantitative or qualitative culture), even in patients with HAP, to narrow the initial spectrum of empirical antibiotic treatment. The recommendation includes retrieving lower respiratory samples before any change in antimicrobial treatment; as such a change significantly reduces the sensitivity and specificity of both qualitative and quantitative samples.

Molecular diagnostic methods that allow for the detection of multiple pathogens and antimicrobial resistance in a single sample could greatly facilitate VAP management, especially in patients with risk factors for multi-drug resistant (MDR) bacteria. These methods are highly sensitive, and if a suspected MDR pathogen is absent with this testing, it is not likely to be present on culture, and antibiotic coverage of that pathogen can be stopped. For example, an RCT[106] investigated whether rapid automated polymerase chain reaction (rPCR) assays that detect meticillin resistant *S aureus* (MRSA) in bronchoalveolar lavage (BAL) samples could safely decrease the use of vancomycin or linezolid for suspected cases of MRSA pneumonia in mechanically ventilated patients (22 patients received antibiotic management based on the rPCR result and 23 other patients continued with routine care). It found that duration of anti-MRSA treatment for the initial suspected episode of MRSA pneumonia was significantly shorter in the intervention group (32 h *v* 72 h, P<0.001). Furthermore, hospital mortality was reported to be 14% and 39% in the intervention and routine care groups, respectively (P=0.06). Similarly, a separate experimental study sought to detect *S aureus* in endotracheal aspirate samples from mechanically ventilated patients using GeneXpert MRSA/*S aureus* endotracheal aspirate (ETA) assay in comparison with two PCR based methods (including GeneXpert) and three culture based methods. It found that the assays had both a sensitivity and specificity of 100% when compared with the other assays, underpinning the value of these new diagnostic techniques in the management of pneumonia. Nonetheless, clinical implementation of these techniques in routine clinical practice is difficult partly because of high costs and a lack of standardization. Also, because of the highly sensitive nature of these techniques, they cannot always distinguish colonization from infection.

The changing etiology of pneumonia

Severe CAP: the emerging role of viruses, community acquired MRSA, and selected Gram negative bacteria

In severe CAP, pneumococcus remains the most commonly identified bacterial pathogen.[59 107-109] However, the past decade has seen an increase in the use of molecular diagnostic techniques that facilitate detection of multiple viruses in one respiratory sample. As a result, respiratory viruses in severe CAP have been reported with increasing frequency.[110-112] Additionally, an increase in the age of patients hospitalized for pneumonia is important, as this population is more susceptible to severe viral infection.[60 113 114] Data from a systematic review and meta-analysis from Europe have shown a prevalence of respiratory viruses of between 20% and 25% of CAP cases[115 116]; these percentages are similar to those reported in studies from the US[110]and Asia.[111]

The US multicenter study,[110] which included 2259 adults with radiographic evidence of pneumonia and specimens available for etiological diagnosis, found that a viral cause was detected in 23% of cases, with rhinovirus and influenza virus being the most common. Bacterial pathogens were detected in 11%, while mixed viral and bacterial pathogens were in 3%. Among the 482 ICU patients included in this study, the most common group of microorganisms included respiratory viruses (22%), followed by bacterial pathogens (19%), and bacterial-viral co-infection (4%). A prospective, multicenter observational study[111] found that, of the 2649 non-immunocompromised adult patients with CAP, viruses were identified in 915 of the 1177 with an etiological diagnosis. Influenza was present in 581 patients, and non-influenza virus in 240. ICU admission occurred in 8.3% and 5.4% owing to influenza virus and non-influenza virus, respectively. Also, the 90 day mortality rates were 3.8% and 1.7%, respectively, with no significant differences.

Similarly, a prospective cohort study that compared the outcomes of hospitalized patients with CAP and influenza with those with and without bacterial co-infection[117] found that those with viral and bacterial co-infection had acute respiratory distress syndrome (ARDS) more frequently than those with pure viral CAP or bacterial CAP (21% viral and bacterial co-infection; 19% viral CAP; and 10% bacterial CAP; P<0.001). They also required ICU admission more often (32% viral and bacterial co-infection; 32% viral CAP; and 13% bacterial CAP; P<0.001) than those with bacterial pneumonia. Interestingly, 30 day mortality did not differ among groups (4% in viral and bacterial co-infection; 3% viral CAP; and 6% bacterial CAP [P=0.232]).

In the ICU, viruses often are present in combination with bacterial pathogens. In one observational study of 49 mechanically ventilated patients with CAP,[118] 49% of cases had a viral etiology, pure or mixed, with rhinovirus and adenovirus the most frequently detected. Sepsis can also complicate viral infections. A retrospective observational study[113] reported that 26% of ICU patients presented with viral sepsis and had an associated ICU mortality of 8%. Moreover, ARDS is another frequent complication in viral pneumonia.[119] One recent study found that respiratory viruses were the causal agent in 11% of mechanically ventilated patients with CAP and ARDS.[120] A prospective observational study[121] investigated the incidence of respiratory viruses in patients admitted to 16 Italian ICUs during the

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2014-15 influenza season. It reported that the influenza A virus was the most frequently detected (83%), followed by human rhinovirus (12%), and RSV and influenza B virus (3% each). A prospective cohort study[122] from Australia and New Zealand reported an increase in ICU admissions resulting in pneumonia and sepsis during the winter and spring of 2017, with influenza virus strain H3N2 being predominant. This rise in ICU admissions was also higher than during the 2009 H1N1 pandemic.

Bacteria such as *S pneumoniae, H influenzae,* and *S aureus* constantly colonize the upper airways, with at least one of these bacteria colonizing approximately 20-50% of healthy individuals. Colonization can also synergize with viral infections to add to poor outcomes.[123 124] In influenza infections, colonization by *S pneumoniae* has been associated with an increased risk of ICU admission and mortality. Colonization by *S aureus* has been associated with an increased risk of mortality in adults, and MRSA co-infection has been associated with severe disease and mortality.[125 126]

However, it is uncertain whether co-detection represents either true co-infection (two or more pathogens that infect the patient at the same time and run the same time course) or sequential infection instead (eg, a preceding viral infection with some residual viral shedding and a secondary bacterial infection). Both scenarios pose a challenge in routine clinical practice. A prior influenza infection is well known to damage epithelial cells, thereby leading to a compromised barrier function of the airway and exposed surface receptors, and favors adhesion of bacteria. An experimental study[127] found that a prior influenza infection increased pneumococcal colonization of the murine nasopharynx and promoted a spread of bacteria into the lungs. It observed that influenza accelerated bacterial replication in vivo, and sialic acid was identified as a host derived metabolite stimulating pneumococcal proliferation. Recent findings regarding innate and adaptive immune system responses during co-infection with influenza virus and *S pneumoniae* or *S aureus* showed that the presence of both microorganisms resulted in dysregulated cytokine and chemokine production. This type of dysregulated production occurred after pattern recognition receptors recognized the pathogen and triggered dynamic changes in immune cell recruitment and activation.[128] A hyperactivated signaling pathway elicits a massive recruitment of immune cells and an overshooting of inflammatory processes, leading to severe lung damage. As a result of such injury, pathogens can penetrate more deeply into the tissue and uncontrolled replication of viral and bacterial pathogens can occur.[128] Also, suppressed immune reactions can take place, owing to lower pathogen clearance which occurs as a result of an inhibition of immune cells or signaling cascades by pathogens. All of these mechanism can explain increased morbidity and mortality in cases of influenza virus and bacterial co-infection.[128 129]

Community acquired MRSA (CA-MRSA) infections are reported globally and are associated with severe outcomes. The estimated incidence is approximately 0.51-0.64 cases per 100 000 inhabitants.[130] Clinical presentation of CA-MRSA includes necrotizing pneumonia, a severe form of pneumonia associated with abscess and cavity formation, and sometimes empyema. CA-MRSA has been reported in healthy, young adults with CAP and no exposure to healthcare settings and leads to poor clinical outcomes and high mortality, especially in those with post-influenza infection. Severe, necrotizing CA-MRSA pneumonia is thought to be caused by the exotoxin Panton-Valentine leukocidin (PVL).[131] PVL is a toxin that causes leukocyte destruction and tissue necrosis.

P aeruginosa, extended spectrum β-lactamase producing *Enterobacteriaceae* and MRSA (PES pathogens) form part of another important microorganism group that causes CAP. Such pathogens account for up to 6% of hospitalized patients with CAP and a microbiological diagnosis; however, current empirical therapy recommendations in guidelines do not target this pathogen group. In 2015, a prospective observational study[132] proposed the PES score to assess the risk of pneumonia owing to PES pathogens. The score showed modest accuracy in validation studies in the general population (AUC 0.81; 95% CI 0.74 to 0.88), ICU population (AUC 0.73; 95% CI 0.61 to 0.86) and in very old patients with CAP (AUC 0.64; 95% CI 0.58 to 0.71).[133] Other scores assessing the potential risk of MDR pathogens in patients with CAP have been published in the past 10 years[134-137] (fig 2).

A prospective, multicenter cohort study[138] assessed an antibiotic strategy based on risk factors for PES pathogens, independent of the site of pneumonia acquisition. Risk factors for PES pathogens included antibiotic therapy in the past 180 days; poor functional status (Barthel index <50 or performance status ≥3); hospitalization for >2 days within the past 90 days; occurrence of pneumonia ≥5 days after admission to an acute hospital; requirement for hemodialysis; and immunosuppression. In a multicenter cohort of 1089 patients (656 CAP, 238 healthcare associated pneumonia, 140 HAP and 55 VAP), patients with 0-1 risk factors for PES pathogens were to receive treatment with standard therapy (a β-lactam plus a macrolide), whereas patients with ≥2 risk factors for PES pathogens were proposed to receive appropriate therapy for HAP (a two or three drug regimen combining an antipseudomonal β-lactam with a quinolone or aminoglycoside plus optional linezolid or vancomycin). Approximately 83% of patients received treatment according to the proposed algorithm, and only 4% had inappropriate treatment. Basing the algorithm on risk factors for PES pathogens and disease severity instead of the site of pneumonia acquisition appeared to simplify antimicrobial treatment and improve the accuracy of empirical treatment. However, this algorithm requires validation in a large population. Table 1 describes the recommendations for therapy of

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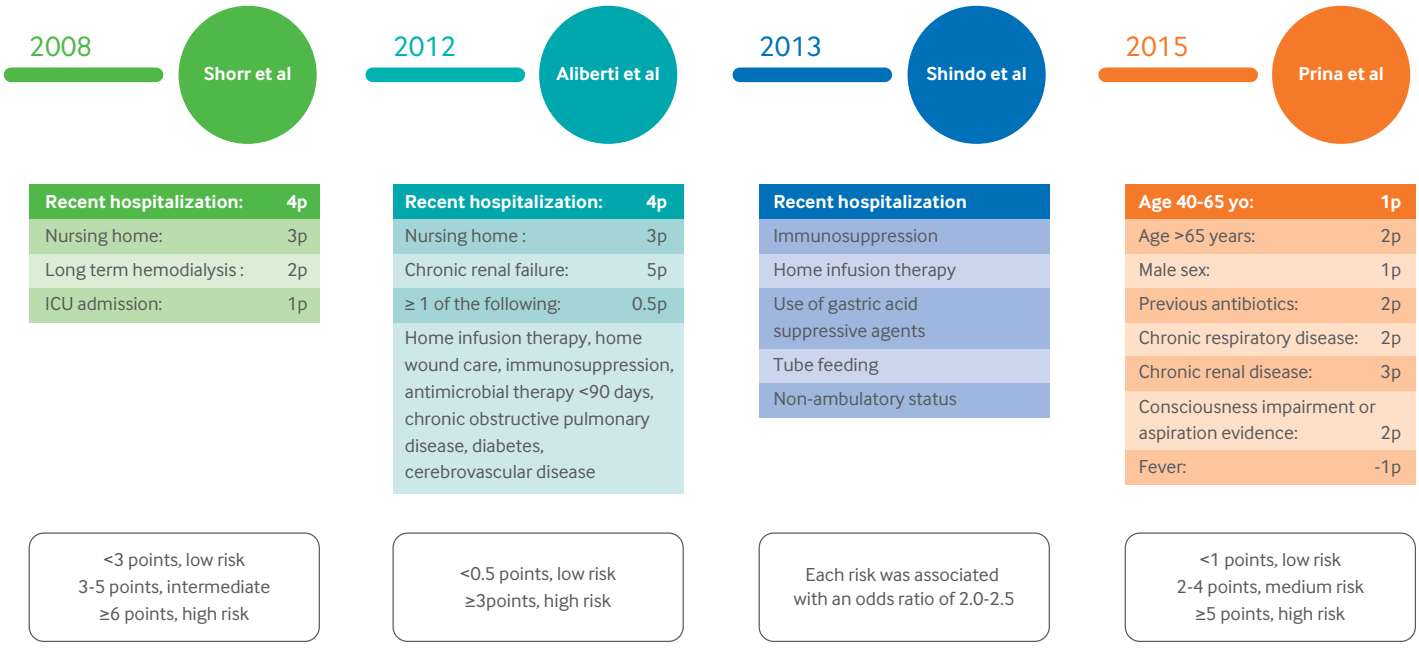

Fig 2 | Prediction of multidrug resistant pathogens in CAP

HAP/VAP proposed by current US and European guidelines, but the principles extend to patients with severe CAP as well, and were used in the algorithm cited above.

It is important to recognize that in patients with CAP, PES pathogens do not have a universal distribution. A limited number of centers have reported this group of pathogens,[132 133 139-142] so clinicians should consider local etiology and resistance patterns.

VAP—the role of MRSA and drug resistant Gram negative pathogens

In the past decade, studies from the US and Europe have reported an increase in the prevalence of MDR pathogens in VAP.[143-145] The most frequent MDR Gram negative pathogens were *P aeruginosa*, *Acinetobacter* spp, and extended spectrum β-lactamase producing *Enterobacteriaceae*. In addition, MRSA is the most frequent MDR Gram positive pathogen. These pathogen groups are associated with poor clinical outcomes, especially because of inappropriate or delayed initial antimicrobial treatment.[146-148]

Current guidelines from ATS/IDSA[5] and the European Respiratory Society, European Society of Intensive Care Medicine, European Society of Clinical Microbiology and Infectious Diseases, and Asociación Latinoamericana del Tórax[7] highlight the importance of administering prompt and adequate empirical treatments based on a patient's risk stratification for MDR pathogens and on local microbiological and antibiotic resistance data (table 2).

US guidelines[5] identify five risk factors associated with MDR pathogens: previous intravenous antibiotic treatment within 90 days; hospitalization for ≥5 days before the occurrence of VAP; septic shock at the time of VAP; ARDS preceding VAP; and the need for renal replacement treatment before VAP onset. Interestingly, a prospective cohort study[149] found that in using these risk factors for MDR pathogens, sensitivity was high, yet specificity was very low and overall performance poor, which could lead to excessive broad spectrum empirical antimicrobial treatment. Among the five risk factors, only antibiotic use in the past 90 days (negative predictive value of 79%) and ≥5 days of hospitalization (negative predictive value of 80%) before pneumonia were strongly associated with the presence of MDR

Table 1 | Empiric treatment according to US And European guidelines

Risk for MDR pathogens	US guidelines	European guidelines
Low	Single, narrow spectrum antibiotic with activity against non-resistant Gram negative microorganisms	**(≤15% mortality risk, low MDR risk)** Narrow spectrum antimicrobial with activity for meticillin susceptible *S aureus* and non-resistant Gram negatives: ertapenem, ceftriaxone, cefotaxime, moxifloxacin, levofloxacin
High	Dual antibiotic treatment against Gram negative microorganisms. MRSA coverage if ›10-20% of *S aureus* isolates are MRSA	**(›15% mortality risk and/or high MDR risk)** No septic shock: monotherapy with broad spectrum agent active against ›90% of likely Gram negative pathogens +/- MRSA (if › 25% of *S aureus* isolates are MRSA) Septic shock: combination therapy with anti-pseudomonal regimen +/- MRSA (if › 25% of *S aureus* isolates are MRSA)

Both guidelines agree on stratifying patients according to individual and local community risk factors for MDR pathogens.[6]

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Table 2 | High risk of MDR pathogens in HAP/VAP	
European guidelines (2017)	US guidelines (2016)
Previous antibiotic treatment	Previous antibiotic treatment
≥5 days of hospitalization	≥5 days of hospitalization
Septic shock	Septic shock
Hospital settings with high rates of MDR pathogens (>25%)	ARDS before VAP
Previous colonization by MDR Pathogens	Acute renal replacement therapy before initiation of VAP
Mortality risk >15%	

VAP=ventilator associated pneumonia; ARDS=acute respiratory distress syndrome; HAP=hospital-acquired pneumonia; MDR=multidrug resistant.[4;6]

pathogens. The presence of ARDS preceding VAP had a negative predictive value of 71% for the presence of MDR pathogens. European guidelines[7] do not include renal replacement treatment or ARDS in the definition of patients at high risk for MDR microorganisms. For this reason, in addition to individual patient risk factors, European guidelines include hospital settings with high rates of MDR microorganisms (>25% of all ICU pathogens are MDR), local patterns of resistance, and prior colonization by MDR microorganisms as determinants of risk for such pathogens.

Treatment

CAP guideline recommendations

The ATS/IDSA CAP guidelines were published in 2019[6] and included changes from previous recommendations.[12] Most notably, the guidelines recommended eliminating the category of healthcare associated pneumonia (HCAP), to avoid overuse of empiric broad spectrum treatment. The incidence of resistant pathogens was low enough, even among those with severe CAP, and administering broad spectrum therapy for all those with HCAP led to its overuse. Patients with HCAP who faced high CAP mortality generally had clinical features and multiple comorbidities that affected survival, rather than the mere presence of risk factors for resistant pathogens. Furthermore, reports about adverse outcomes, such as an increase in infections related to *Clostridium difficile*, was associated with the overuse of broad spectrum antibiotics.[135 150 151]

Initial choice of antibiotic

For most patients with severe CAP, initial treatment includes the combination of a β-lactam plus a macrolide or fluroquinolone. For patients without MRSA and pseudomonal risk factors, the β-lactam could be cefotaxime, ceftriaxone, ampicillin-sulbactam, or ceftaroline.[6] For those with pseudomonal risk factors, pathogen coverage could be achieved with a β-lactam such as piperacillin/tazobactam, cefepime, ceftazidime, imipenem, or meropenem. In patients who have a β-lactam allergy, aztreonam is an alternative. Newer β-lactams with activity against more resistant Gram negative pathogens are discussed below.

How to select broad spectrum antibiotics

In severe CAP, evidence suggests that the combination of β-lactam plus macrolide significantly improves the prognosis of patients, compared with non-macrolide regimens.[152-155] A retrospective observational study reported that patients with severe pneumonia had lower rates of 14 day (8% *v* 27%, P=0.02) and 30 day (18% *v* 37%, P=0.05) mortality with combination therapy of β-lactam plus macrolides than with flouroquinolones.[154] Similarly,[153] a prospective multicenter observational study assessed 257 intubated patients with severe CAP, in which 20% of patients received monotherapy and the remaining 80% combination therapy. After the authors adjusted for severity, the use of macrolides was associated with lower ICU mortality (hazard ratio 0.48, CI 95% 0.23 to 0.97, P=0.04) when compared with patients receiving fluoroquinolones. The authors recommended combination therapy with macrolides in intubated patients with severe CAP. A meta-analysis that comprised 9850 critically ill patients with CAP[155] observed that combination therapy with a macrolide and β-lactam (21% *v* 24%; risk ratio 0.82; 95% CI 0.70 to 0.97; P=0.02) was associated with reduced mortality when compared with other regimens. A prospective cohort study that included 1131 patients with CAP[152] found that combination treatment based on pneumonia severity index (PSI) and CURB-65 score[12 22 23] did not significantly reduce 30 day mortality in either group. However, combination therapy based on the ATS/IDSA criteria significantly reduced 30 day mortality in patients with severe pneumonia (odds ratio (OR) 0.12, 95% CI 0.007 to 0.57), albeit not in cases of non-severe pneumonia (OR 1.85, 95% CI 0.51 to 5.40).

An advantage of combination therapy is its ability to cover atypical pathogens, as well as a potential benefit from the immunomodulatory effect of macrolides to attenuate bacterial virulence factors and an excessive systemic inflammatory response. An experimental study[156] found that macrolides inhibit pneumolysin production, even in macrolide resistant strains of pneumococcus. Pneumolysin promotes the extra-pulmonary spread of pneumococcus, which can, in turn, cause cardiac damage.[57] Furthermore, when used as a part of combination therapy,[157] macrolides reduced mortality in patients with severe CAP, especially in those with pneumococcal bacteremia.[158 159] A prospective, multicenter and international study analyzing 844 cases of pneumococcal bacteremia[159] found that combination therapy was associated with a lower 14 day mortality rate (23% *v* 55%, P=0.015).

Optimal treatment for MRSA

Unlike nosocomial MRSA, CA-MRSA is susceptible to clindamycin, TMP-SMX, and doxycycline.[160]

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Clindamycin and linezolid can inhibit toxin production, which blocks bacterial protein synthesis.[160] According to the ATS/IDSA guideline recommendations,[6] antimicrobial therapy for MRSA should only be used when patients have risk factors for MRSA (prior respiratory isolation of MRSA; recent hospitalization [in the last 90 days], and use of parenteral antibiotics [in the last 90 days], and locally validated risk factors for MRSA). Clinicians should also obtain samples for cultures and perform nasal PCR testing to guide decisions regarding whether to de-escalate or continue treatment.[161 162]

Options for empirical therapy for MRSA include vancomycin 15 mg/kg/12 h (adjustments made based on levels) or linezolid 600 mg/12 h. In patients with severe necrotizing CAP, it may be necessary to add an anti-toxin to treatment, such as adding clindamycin to vancomycin or using linezolid (which also has anti-toxin activity) alone. Linezolid penetrates the lung better than vancomycin, but clinicians more commonly administer it in HAP and VAP than in CAP.

Antiviral agents

Viral pneumonia is recognized as a common cause of severe CAP, and many patients have mixed viral and bacterial infections. The ATS/ISDA guidelines recommend using anti-influenza treatment (oseltamivir) in all patients with documented severe influenza, regardless of symptom duration, although the benefit is greatest if given within the first 48 hours.[6] In addition, because of a high incidence of bacterial co-infections, antibiotic treatment is recommended in confirmed influenza infections, especially to cover for pneumococcus and *S aureus*. However, de-escalation of antibiotics is recommended in patients who show no evidence of bacterial co-infection and show clinical stability after 48-72 hours of antibiotic treatment.[6]

In patients with covid-19, bacterial pneumonia has sometimes been observed alongside viral pneumonia.[163 164] Most patients with lung infiltrates initially receive antibiotics, with discontinuation of such treatment occurring based on clinical assessment and serial measurements of biomarkers such as procalcitonin.[165 166] For hospitalized patients with covid-19, the antiviral agent remdesivir has shown some benefit, particularly during the early course of the disease, as have monoclonal antibodies (especially in early stage disease and outpatients).[167] Data from two large randomized controlled trials on the use of remdesivir in covid-19 showed varying results. The ACT-1 trial[168] found that remdesivir was superior to placebo in shortening the time to recovery in hospitalized adults with covid-19, while the SOLIDARITY trial[169] reported no mortality benefit. Currently, remdesivir is recommended for patients with severe covid-19 who require oxygen therapy, excluding mechanical ventilation or extracorporeal membrane oxygenation.[170]

For other viral pneumonias in immune competent hosts, antiviral agents are not routinely administered.

Corticosteroids

Corticosteroids have immunomodulatory properties and are frequently used as adjunctive therapy in severe pneumonia because of their anti-inflammatory effects. Controversy still surrounds their use, but data from some studies have shown that the use of glucocorticoids reduces mortality in patients with severe CAP, especially in those with a high level of systemic inflammation.[171 172] However, this effect has yet to be seen in patients with non-severe pneumonia.

In a multicenter, randomized, double blind and placebo controlled trial study investigating the effect of corticosteroids on treatment failure in 120 patients with severe CAP (61 received methylprednisolone and 59 were control cases) and a high inflammatory response (initial levels of C reactive protein (CRP) >15 mg/dL), treatment failure was reported to be less frequent in the group receiving corticosteroids (13%) when compared with the placebo group (31%) (P=0.02). However, in-hospital mortality was similar between both groups (10% *v* 15%; P=0.37). The study concluded that the use of low dose corticosteroids (0.5 mg/kg every 12 hours for five days) decreased treatment failure in patients with severe CAP and a high inflammatory response, when compared with placebo.[171]

Another systematic review and meta-analysis,[172] including data from 1506 patients (748 patients were randomized to corticosteroids and 758 patients to placebo) from six trials reported that the use of corticosteroids in hospitalized patients with CAP reduced the time to clinical stability (adjusted difference, -1.03 days; 95% CI -1.62 to -0.43 days; P=0.001) and length of hospital stay (-1.15 days; 95% CI -1.75 to -0.55 days; P<0.001) by approximately one day without any effect on mortality (OR, 0.75; 95% CI 0.46 to 1.21; P=0.24). However, the authors also reported an increased risk for CAP related re-hospitalization (OR 1.85, 95% CI 1.03 to 3.32, P=0.04) and hyperglycemia (OR 2.15; 95% CI 1.60 to 2.90, P<0.001).

Data from two randomized clinical trials[173 174] support the use of hydrocortisone as adjunctive therapy in patients with septic shock. The randomized Adjunctive Corticosteroid Treatment in Critically Ill Patients with Septic Shock trial [173] included 3658 patients with septic shock undergoing mechanical ventilation (1832 patients randomized to hydrocortisone group and 1826 to the placebo group). The participants received either hydrocortisone at a dose of 200 mg per day or placebo for seven days or until death or ICU discharge. The authors reported that the use of hydrocortisone in this population did not result in a lower 90 day mortality when compared with patients who received placebo (OR, 0.95; 95% CI 0.82 to 1.10; P=0.50). A multicenter, double blind and randomized trial[174] evaluating the effect of hydrocortisone plus fludrocortisone treatment against a placebo in 1241 patients with septic shock (614 randomized to hydrocortisone plus fludrocortisone and 627 to placebo) reported that 90

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day all-cause mortality was lower in patients who received hydrocortisone plus fludrocortisones (43% *v* 49%, P=0.03).

Conversely, several studies observed that the use of corticosteroids in influenza may be associated with a significantly higher mortality rate possibly resulting from superinfection.[175-177] Despite these concerns, recent studies of severe covid-19 pneumonia with respiratory failure have shown a mortality benefit, particularly in the controlled, open label Randomized Evaluation of COVID-19 Therapy trials, which included the administration of 6 mg of dexamethasone daily for 10 days[178] in patients on oxygen or mechanical ventilation.

The ESCAPe trial (NCT01283009) investigated the use of methylprednisolone (20 days of treatment: seven days (40 mg/day), seven days (20 mg/day), and six days (12 mg/day and 4 mg/day) versus placebo in 583 critically ill adult patients with CAP, with the primary study outcome being 60 day mortality. The mean age of patients was 68.8 years and mean PSI was 124 patients. Of these, 96% were male and 33% were on ventilation. With respect to 60 day mortality, the results showed no differences in superiority between methylprednisolone and placebo (OR 0.90; 95% CI 0.58 to 1.40, P=0.635).[179]

Current recommendations in international guidelines on the use of corticosteroids as adjunctive therapy are to not administer them routinely in patients with either non-severe CAP or severe influenza pneumonia. However, corticosteroids may prove valuable in patients with severe pneumonia with refractory septic shock or a high systemic inflammatory response, as well as in those with pneumococcal CAP with meningitis.[6]

Immunoglobulin treatment

Some studies have shown lower levels of circulating immunoglobulins in patients admitted to ICU with severe pneumonia when compared with non-ICU patients, as well as an association between these lower levels of immunoglobulins and increased mortality.[180 181] These data suggest a possible role of immunoglobulins in adjunctive treatment for severe CAP.

In a single center observational study[182] investigating the role of immunoglobulin levels (IgG, IgA, IgM) in 362 patients with CAP (172 ward and 190 ICU) and their impact on outcomes, IgG2 levels <301 mg/dL were associated with worse prognosis. Furthermore, low concentrations of IgG2 were an independent marker of ICU admission and mortality. Similarly, a separate single center observational study[181] reported that IgM concentrations were inversely associated with severity and a protective factor against mortality in cases of severe influenza CAP.

The efficacy of immunoglobulins was investigated as an adjunctive therapy in mechanically ventilated patients with severe CAP and septic shock.[183] In an observational study of 1324 patients receiving immunoglobulins as adjunctive therapy and 6940 controls, no significant association was seen between adjunctive therapy and mortality. Similarly, another post hoc subgroup analysis of data from a retrospective cohort study including 960 patients with sepsis and septic shock found no association between the use of low dose IgG immunoglobulins as adjunctive therapy and decreased ICU (21% *v* 18%, P=0.185) or in-hospital mortality (34% *v* 31%, P=0.066).[184]

Additionally, a double blind phase II study[185] published data on 160 patients with severe pneumonia and requiring invasive mechanical ventilation, who were randomized to trimodulin (a polyclonal antibody preparation containing IgM, IgA, and IgG) or placebo for five consecutive days. Treatment with trimodulin did not increase ventilator-free days when compared with patients in the placebo group (median days 11 *v* 8, P=0.173). Interestingly, the authors observed that a subset of patients with elevated CRP and/or lower IgM levels had reduced mortality and an increase in ventilator-free days, with trimodulin treatment.

VAP guideline recommendations

In the past decade, the increased incidence of MDR pathogens reported in VAP has complicated management, and infection caused by these organisms has been associated with worse outcomes.[147 148] Local epidemiology and susceptibility information should guide empiric treatment for VAP, in conjunction with a careful assessment of patients' risk factors for MDR pathogens.[5] Risk factors for MDR pathogens differ between US[5] and European[7] guidelines; however, when considering empiric therapy, local bacteriology and resistance patterns remain important, as does prior antibiotic treatment (table 2).

Combination therapy—why and when

In general, local antibiotic susceptibility patterns and the likelihood of MDR, Gram negative, or mixed Gram positive and Gram negative infections guide the choice between monotherapy and combination therapy.

According to US guidelines,[5] if the patient has no risk factors for specific MDR pathogens, such as *P aeruginosa* or MRSA, and receives treatment in an ICU with a low prevalence of MDR microorganisms (<10%), the use of a single, narrow spectrum antibiotic with activity against non-resistant Gram negative microorganisms is recommended (weak recommendation, low quality evidence). Following European guidelines, the use of narrow spectrum antibiotics active against non-resistant Gram negative microorganisms is recommended for patients with a low risk of both MDR microorganisms and mortality who receive treatment in an ICU with a low prevalence of MDR microorganisms (<25%) (weak recommendation, very low quality evidence).[7]

The use of dual antibiotic treatment is recommended in patients presenting with a high risk of MDR pathogens. A systematic review and meta-analysis [186] compared monotherapy and combination therapy

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as empiric treatment for patients with VAP. The study included data of 41 trials and 7015 patients. No significant differences were noted in mortality between both regimens. The authors reported that the ceftazidime-aminoglycoside combination was inferior to meropenem (relative risk (RR) 0.70; 95% CI 0.53 to 0.93). Mortality and treatment failure rates for monotherapy and combination regimen were similar (RR for mortality with monotherapy, 0.94; 95% CI 0.76 to 1.16; and RR for treatment failure with monotherapy 0.88; 95% CI 0.72 to 1.07). The authors highlighted the small proportion of VAP cases caused by MDR pathogens as possibly explaining the lack of benefits of combination therapy. A randomized controlled trial[187] comparing empiric monotherapy with meropenem versus ciprofloxacin plus meropenem for suspected VAP showed no significant differences in 28 day mortality between groups (RR 1.05, 95% CI, 0.78 to 1.42, P=0.74). Furthermore, no differences were noted regarding length of ICU and hospital stay, treatment response, and emergence of antibiotic resistant bacteria. However, the study excluded patients known to be colonized or infected with *Pseudomonas* or MRSA. Interestingly, the authors analyzed cases (n=56) that had infection caused by *Pseudomonas* species, *Acinetobacter* species, and MDR Gram negative bacilli. They observed a higher likelihood of adequate initial therapy (84.2% *v* 18.8%, P=0.001) and microbiological clearance (64.1% *v* 29.4%, P=0.05) when a combination regimen of meropenem plus ciprofloxacin was administered to those with resistant organisms, compared with monotherapy. Similarly, a systematic review,[188] including data from 12 randomized controlled trials and 3571 patients with VAP, found no significant difference in all-cause mortality (OR 0.97, 95% CI 0.73 to 1.30), clinical recovery (OR 0.88, 95% CI 0.56 to 1.36), and length of ICU stay (mean difference 0.65, 95% CI 0.007 to 1.23) between monotherapy and combination therapy. However, the authors acknowledged that these data may not be generalizable to all patient groups, given that the study did not identify patients with an increased risk of MDR bacteria. Additionally, in cases caused by MDR bacteria, results from observational studies[189-192] showed combination regimens including broad spectrum β-lactam with an aminoglycoside increased the percentage of appropriately treated cases when compared with monotherapy or a combination regimen of a β-lactam and fluoroquinolone.

US guidelines recommend the use of dual antibiotic treatment against Gram negative microorganisms for patients with a high risk of an MDR microorganism; those with lung disease; and those treated in an ICU with either an unknown or high prevalence of MDR pathogens (>10%) (weak recommendation, low quality evidence). If the patient is also at risk for an MRSA infection, treatment for this pathogen is added. Conversely, European guidelines recommend a broader spectrum approach in empiric antibiotic treatment if the patient is in an ICU with a high prevalence of MDR microorganisms (>25%) and/or at high risk of MDR microorganisms and mortality. Specific choices are then guided by the hemodynamic status of the patient. In individuals with no septic shock at diagnosis, monotherapy is considered adequate, provided that the agent is active against >90% of common Gram negative organisms in the ICU setting. Broad spectrum, multidrug treatment is recommended for patients with septic shock. However, this therapy should provide coverage for *P aeruginosa*, *Enterobacteriaceae* with extended spectrum β-lactamases, and *A baumannii* (if highly prevalent in the ICU) (strong recommendation, low quality evidence). The rationale for combination therapy is to provide sufficiently broad spectrum coverage to make appropriate treatment more likely than with monotherapy. In addition, combination therapy could eradicate organisms more quickly than monotherapy, being associated with a survival advantage over monotherapy for patients with septic shock and a mortality risk >25%.[7 193]

Treatment for MDR pathogens: MRSA, Pseudomonas, Acinetobacter

Use of empiric anti-MRSA antimicrobials should be decided based on epidemiological data. The ATS/ISDA guidelines[5] suggest their use if >10-20% of *S aureus* isolates are MRSA, whereas European guidelines[7] suggest use if >25% of *S aureus* isolates are MRSA. For patients with a high risk of MDR pathogens or those treated in an ICU setting with >10% of Gram negative pathogens resistant to the best monotherapy option, European guidelines[7] suggest the use of two anti-pseudomonal agents from two separate classes.

The US guidelines[5] divide high risk patients into two main groups: (1) patients with a high risk of MDR pathogens and no septic shock who can receive a single broad spectrum agent active against >90% of Gram negative-likely microorganisms, and (2) patients with a high risk of MDR pathogens and septic shock who should receive a dual anti-pseudomonal regimen, with coverage for *Acinetobacter* spp and ESBL-producing *Enterobacteriaceae* if such pathogens are prevalent in the local antibiogram.

In recent years, new therapeutic options have become available for HAP/VAP, especially targeting MDR pathogens:

1. Ceftazidime-avibactam (CEF/AVI) is a combination of a third generation cephalosporin with a non-β-lactam β-lactamase inhibitor. CEF/AVI is active against a variety of β-lactamases, including Ambler Class A (*K pneumoniae* carbapenemases and ESBL-type enzymes), Ambler Class C, and some Ambler-class D serine enzymes (eg, oxacillinase oxa-48). However, it is not active against metallo-β-lactamases or Acinetobacter oxa-like carbapenemases. Ceftazidime-avibactam received approval by the Food and Drug Administration (FDA) and European Medicines Agency (EMA) for use in HAP/VAP. The combination regimen was shown to be non-inferior to meropenem in a randomized

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controlled trial of carbapenem resistant, non-*Enterobacteriaceae* pneumonia.[194]

2. Ceftolozane-tazobactam (CEF/TAZ) is a cephalosporin and β-lactamase inhibitor with in vitro activity against multidrug resistant *P aeruginosa* and ESBL-producing *Enterobacteriaceae*. Results from a randomized controlled double blind, non-inferiority trial including 726 mechanically ventilated patients with Gram negative nosocomial pneumonia[195] compared CEF/TAZ (2 g ceftolozane plus 1 g tazobactam infused for 1 hour every 8 hours) (362 subjects in the ceftolozane-tazobactam group) with meropenem (1 g infused for 1 hour every 8 hours) (364 subjects in the meropenem group). In the study, both drugs were equivalent and well tolerated in mechanically ventilated patients with Gram negative nosocomial pneumonia. However, CEF/TAZ had a mortality advantage in those with ventilated HAP and those with previously unsuccessful antibiotic treatment for the current nosocomial pneumonia episode. This new antibiotic has received approval by the FDA and EMA for HAP treatment.[196 197]

3. Meropenem-vaborbactam is a combination agent containing an existing β-lactam antibiotic (meropenem) with a cyclic boronate non-β-lactamase inhibitor (vaborbactam) and is active against Gram negative microorganisms, including those with extended spectrum β-lactamases and *K pneumoniae* carbapenemases. However, it is not active against metallo-β-lactamase and oxacillinase producing strains. Although not approved for VAP, meropenem-vaborbactam showed an advantage for clinical recovery, when compared with the best available therapy (usually colistin), in a trial that included mechanically ventilated patients with carbapenem resistant *Enterobacteriaceae*.[198]

4. Imipenem-relebactam (IR) is a combination agent containing an existing β-lactam antibiotic (imipenem-cilastatin) with non-β-lactam β-lactamase inhibitor (relebactam) and is active against Gram negative microorganisms, including Ambler class C, extended spectrum β-lactamases and *K pneumoniae* carbapenemases. However, it is not active against metallo-β-lactamase and oxacillinase producing strains. In a phase III trial that compared IR with pipercillin-tazobactam in 537 patients with nosocomial pneumonia, with half of the patients being mechanically ventilated, both therapies were equivalent in clinical recovery and mortality.[199] Survival was, however, higher in the subgroup of those mechanically ventilated at baseline when they received IR.[199]

5. Cefiderocol is a siderophore cephalosporin that binds to iron and enters the bacterial cell, using the iron transport system. It is active against a wide range of carbapenem resistant pathogens including *Enterobacteriaceae, P aeruginosa,* and *Acinetobacter baumanii*. It is also active against *Stenotrophomonas maltophilia*. Cefiderocol is approved for nosocomial pneumonia, including VAP, but has shown no survival advantage or higher recovery rates when compared with meropenem. In a separate study, patients with VAP had a lower survival than with the best available therapy.[200 201]

Using pharmacokinetic/pharmacodynamic principles to optimize dosing

Applying pharmacokinetic/pharmacodynamic (PK/PD) principles to antibiotic dosing and delivery regimens may improve the outcomes of patients with pneumonia. Drugs that kill bacteria in a concentration dependent fashion (aminoglycosides) have their efficacy maximized in relation to how high a high peak concentration they achieve, relative to minimum inhibitory concentration (MIC) of the target pathogen, in the serum and at the site of infection. This can be optimized when the entire 24 hour dose is administered as a single infusion.[185 194] Conversely, β-lactams (penicillins, cephalosporins, carbapenems) reach their optimal bactericidal effect in relation to how long the concentration stays above the MIC of the target pathogen and this can be optimized by using a prolonged or continuous infusion.[131 195] For example, continuous infusion of vancomycin was associated with better outcomes,[202 203] while higher doses and a continuous infusion of linezolid led to improved outcomes, especially in patients with ARDS and infections caused by resistant pathogens.[204 205]

Aerosolized antibiotics

Aerosolized antibiotics can deliver higher antibiotic concentrations in the lung parenchyma and have less systemic toxicity than intravenous treatment, yet no recommendations call for their use as routine adjunctive therapy in VAP. Three randomized trials have investigated the use of adjunctive nebulized antibiotics in patients with VAP[206-209]: the IASIS trial (aerosolized adjunctive amikacin and fosfomycin in patients with VAP and suspected MDR, Gram negative bacteria); the INHALE trial (inhaled amikacin as adjunctive therapy in patients with VAP and suspected MDR, Gram negative bacteria); and the VAPORISE trial (inhaled tobramycin as adjunctive therapy in patients with VAP). All three studies showed negative results for improved clinical outcomes or mortality.

In 2019, results from a meta-analysis by the ATS/IDSA HAP guideline committee, which included nine studies of inhaled antibiotics for VAP treatment,[210] showed that the use of inhaled antibiotics was beneficial in treating VAP caused by difficult-to-treat microorganisms. The ATS/IDSA guidelines[5] therefore recommend adding inhaled antibiotics to systemic antibiotics in cases of Gram negative pneumonia caused by MDR microorganisms. Inhaled colistin should be used instead of polymyxin B. Inhaled antibiotics are also recommended as a last resort for patients with VAP and sensitive or resistant microorganisms who are not responding to treatment. European guidelines[7] do not recommend the use of inhaled antibiotics until more data have become available.

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Treatment duration for CAP and HAP

Data from two meta-analyses showed that short course antibiotic therapy (five to seven days) may be adequate in treating patients with CAP.[211 212] In the first meta-analysis of 19 randomized controlled trials including data of 4861 patients and irrespective of severity of pneumonia, the authors did not find any differences regarding clinical recovery rates between short (≤6 days) and long course treatments (≥7 days).[211] Furthermore, short course treatment was associated with fewer, serious adverse events (RR=0.73; 95 CI 0.55 to 0.97) and potentially lower mortality than long course treatment (RR=0.52; 95% CI 0.33 to 0.82). A second meta-analysis analyzing data from seven randomized controlled trials including 3021 patients[212] showed that short course antibiotic treatment (five days) in adults with bacterial CAP achieved clinical responses similar to those observed in patients receiving long course antibiotic therapy (7 to 14 days). The authors also reported that all-cause mortality did not differ in relation to duration of antibiotic treatment, and short course antibiotic therapy was associated with a lower rate of adverse effects.

According to the ATS/IDSA guidelines,[6] a patient's clinical stability should guide duration of antibiotic treatment, with it being no less than five days. The guidelines also state that longer courses of antibiotics are recommended in cases of pneumonia complicated by meningitis, endocarditis, and other deep seated infections. In cases of infection by other, less common pathogens, guidelines do not specify duration of treatment.[6]

For patients with VAP, US guidelines[5] recommend a seven day course of antibiotic treatment. Depending on the rate of improvement of clinical, radiological, and laboratory parameters; however, some patients may require a shorter or longer duration of antibiotics. European guidelines[7] recommend a 7-8-day course of antibiotic treatment in patients who are not immunodeficient, do not present with cystic fibrosis or other pulmonary complications (empyema, lung abscess, cavitation, or necrotizing pneumonia); received appropriate treatment initially; do not have a highly resistant pathogen (*P aeruginosa*, carbapenem resistant *Acinetobacter* spp, carbapenem resistant *Enterobacteriaceae)*; and respond well to antibiotic treatment.

Biomarkers

Biomarkers provide information about host response to infection and pharmacological intervention; however, heterogeneous immunological and inflammatory responses in patients with pneumonia make their universal use challenging.[213 214] Biomarkers, such as (CRP), procalcitonin (PCT), lymphocytes, red blood cell distribution, interleukin-6, pro-adrenomedullin, N-terminal pro-B-type natriuretic peptide, soluble triggering receptor expressed on myeloid cells-1, co-peptin, and soluble form of urokinase-type plasminogen activator receptor have been studied.[214-222]

In clinical practice, CRP, PCT, and, more recently, lymphocytes are the most frequently used biomarkers to guide duration of antibiotic treatment and prognosis in pneumonia.

CRP is a major acute phase protein produced by macrophages in response to any type of inflammation, including bacterial and viral infections. It is released between four and six hours after acute injury, peaking at around 36-48 hours. However, CRP has low specificity in pneumonia diagnosis, as levels can be high owing to other clinical causes, such as neoplasia or autoimmune diseases.[223]

PCT is a peptide precursor of the hormone calcitonin that is synthesized in the thyroid gland. It increases during inflammatory and infectious diseases, primarily as an acute phase reactant produced in the liver. In healthy individuals, plasma concentrations of PCT are very low (<0.1 ng/mL); however, levels rise with bacterial infections.[223]

Although no PCT threshold has been found to discriminate specifically between viral and bacterial infection for adults hospitalized with CAP,[224] higher levels suggest an increased probability of bacterial infection.

Interestingly, results from secondary analyses of data from two prospective longitudinal cohorts [225] reported that the time from symptom onset in pneumonia to initial healthcare presentation may affect levels of CRP and PCT. The study included 541 patients with CAP, divided into two groups based on the time to symptoms: early presenters (<3 days since symptom onset) and late presenters (>3 days). In the study, CRP and PCT were lower in early presenters, suggesting that the time to presentation may influence the interpretation of these biomarkers. The authors also propose considering CRP as possibly a more useful biomarker in patients with a longer duration of symptoms; in patients with symptoms lasting ≤48 hours, PCT might hold better utility.

In patients with CAP, PCT has been studied as a tool to reduce duration of antibiotic treatment. Several RCTs have used serial PCT measurements to determine duration of antibiotic treatment, showing reduced treatment duration. However, control group participants who received standard treatment had antibiotic treatment courses lasting much longer than seven days[226-229] and exceeding guideline recommendations.

Current international guidelines recommend initiating antimicrobial treatment based on clinical suspicion in radiographically confirmed CAP and not on the basis of PCT levels.[6] Interestingly, studies have reported a correlation between higher levels of CRP and PCT and an increased risk of complications, admission to ICU, and short term mortality.[216 230-232]

A large meta-analysis of 26 studies on duration of antibiotic treatment in respiratory infections (CAP, HAP, VAP, exacerbations of COPD, and bronchitis)[233] found that treatment duration guided by PCT was associated with a reduction of 2.4 days of treatment (5.7 *v* 8.1 days, P<0.001). Further, lower mortality was observed in the group that received PCT guided

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antibiotic treatment (OR 0.83, 95% CI 0.70 to 0.99, P=0.037). These benefits applied to patients with both CAP and VAP in the ICU. The recommendation set forth in European HAP/VAP guidelines[7] is to use serial PCT measurements in conjunction with clinical assessment to shorten duration of antibiotic treatment in pneumonia cases that required a prolonged course of treatment.

More recently, a study[213] investigated the value of lymphocytes as a biomarker of severity and found that lymphopenia conferred an increased risk of severity in patients with CAP, and that adding lymphocyte count to the CURB-65 score improved predictions of 30 day mortality. Another study from China[234] reported that the combination of PO_2/FiO_2 and lymphocyte count predicted mortality and ICU admission in hospitalized patients with influenza pneumonia. The authors found that the likelihood of severe influenza pneumonia was high in patients with $PO_2/FiO_2 \leq 250$ or peripheral blood lymphocyte count $<0.8\times10^9$/L. Lymphocyte count was also studied as a biomarker in ICU acquired pneumonia (ICU-AP). A study from Spain of 473 patients reported that lymphocytopenia was an independent predictor of 90 day mortality in non-immunocompromised patients.[235] Lymphocyte count is simple and a non-costly biomarker that could prove useful, especially in hospitals where other biomarkers are not available; utility of this biomarker has been shown in severe CAP and in immunocompromised patients with ICU-AP.

Despite the promising value of CRP and PCT, limitations remain to biomarker use in daily practice. Biomarkers should be viewed as an adjunctive tool in clinical evaluations and decision making processes related to site of care and treatment duration.

Pneumonia prevention

CAP prevention focuses on vaccinations, and not so much on those at risk of severe pneumonia. This discussion will center on VAP and measures aimed at reducing the incidence of infection and improving the clinical course, with emphasis on interrupting disease pathogenesis. Currently, preventing colonization with pathogenic bacteria and modification of aspiration remain at the forefront of VAP prevention measures. Some of the most studied preventive measures in VAP include head-of-bed elevation, decreased duration or avoidance of mechanical ventilation, early mobilization, endotracheal tube cuff design, aspiration of subglottic secretions, oral care, and the use of probiotics.

Ventilated patients in the supine position (head elevation between 0° and 10°) have an increased risk of aspiring gastric contents when compared with patients in a semi-recumbent position (head of bed elevation between 30° and 45°).[236-238] In 2016, a review and meta-analysis[238] including eight RCTs comprising 759 patients compared a supine position with a semi-recumbent position. The authors found that the semi-recumbent position significantly reduced the risk of suspected VAP when compared with supine position (14% *v* 40%, RR 0.36; 95% CI 0.25 to 0.50). However, no significant difference was found in the occurrence of microbiologically confirmed VAP. A retrospective cohort study including 5539 patients undergoing mechanical ventilation for at least three days[239] reported that head-of-bed elevation, as well as measures such as sedative infusion interruptions, spontaneous breathing trials, and thromboprophylaxis, was associated with less time to extubation. The lateral Trendelenburg and semi-recumbent position were compared in a RCT[240] that included 395 patients (194 patients in the Trendelenburg position and 201 in the semi-recumbent position). The study showed that the semi-recumbent position was associated with a higher incidence of VAP than the lateral Trendelenburg position (4% *v* 0.5%; RR 0.13; 95% CI 0.02 to 1.03; P=0.04). No differences were seen in microbiologically confirmed VAP and mortality. However, this trial was stopped early due to adverse events in patients randomized in the lateral Trendelenburg position.

Head-of-bed elevation to a semi-recumbent position is a frequent intervention practiced as a preventive measure against VAP.[241 242]

Micro-aspiration of oropharyngeal secretions owing to invasive mechanical ventilation is the main risk factor for VAP.[243-245] Avoiding mechanical ventilation,[246-249] decreasing the time of intubation,[250] and spontaneous breathing trials[251 252] are effective measures in preventing VAP. Various investigators have evaluated the benefits of modifying shapes and materials of the endotracheal tube cuff as it relates to minimizing fluid leakage into the lungs via the cuff and preventing VAP. Cuffs made from materials such as polyurethane have undergone testing and are shown to fit the shape of the trachea better and thus reduce the flow of fluids to the lungs. In contrast with conventional cylindrical cuffs, newer cuffs are conical in shape and approach the tracheal wall evenly and uniformly at the point of maximum cuff diameter. Nonetheless, results from RCTs and meta-analysis do not support the conclusion that these innovations prevent VAP better than traditional materials and forms.[253-256]

Suctioning of subglottic secretions that pool above the endotracheal tube cuff is associated with lower VAP rates; however, controversy exists about its value in decreasing duration of mechanical ventilation, length of ICU stay, and ventilator associated events.[257-262] A recent systematic review and meta-analysis[263] that included 20 studies (nine systematic reviews and meta-analyses and 20 RCTs) found that drainage of subglottic secretions significantly reduced the incidence of VAP (RR 0.56; 95% CI 0.48 to 0.63, I^2=0%, P=0.841) and mortality (RR 0.88; 95% CI 0:80 to 0:97, I^2=0%, P=0.888). More high quality studies are needed to elucidate the potential contribution of this intervention in ventilated patients. Interestingly, a meta-analysis that investigated the influence of subglottic secretion drainage on the causative microorganisms of VAP

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found a significant association between subglottic secretion drainage and decreased VAP caused by Gram positive cocci and *Hemophilus influenzae* (OR 0.29, 95% CI 0.18 to 0.48; P<0.001). However, no significant differences were seen in VAP caused by non-fermentative bacteria and enterobacteria.[264]

Selective digestive decontamination (SDD) is a prophylactic antibiotic strategy that controls the overgrowth of pathogens in the gut, especially those that are Gram negative and multidrug resistant, using topical oral and gastric antibiotics such as tobramycin, polymyxins, and amphotericin B, along with initial intravenous antibiotics. Previous studies[265 266] of ICU settings with low levels of antibiotic resistance observed that SDD and selective oropharyngeal decontamination (SOD) were associated with improved clinical outcomes. One study[267] reported that SDD was more effective than SOD for preventing infection.

The main concerns surrounding the use of SDD is the increased risk of antibiotic resistance[268] and the effect that antibiotic use may have on patients without bacterial infections. A study[269] showed that the use of SDD resulted in the selection of four resistance genes. It concluded that these results showed a limited risk of SDD in antibiotic resistance. Further, in ICU settings where moderate-to-high prevalence rates of antibiotic resistance pathogens exist, the use of SDD was not observed to be associated with decreased infection rates.[270] In a randomized clinical trial of decontamination strategies for mechanically ventilated patients in the ICU, the SDD strategy was reported not to add more benefit than standard care in ICU settings with a high prevalence of antibiotic resistant microorganisms.[270]

In ICU settings with a low prevalence of antibiotic resistant microorganisms, the SDD strategy was associated with less antibiotic resistance and with improved clinical outcomes. More studies are required in ICU settings with a higher prevalence of resistant microorganisms.

Additionally, the use of chlorhexidine for oral hygiene in patients under mechanical ventilation has been reported to reduce the risk of VAP.[271-274] An RCT[275] found that use of chlorhexidine 2%, in comparison with chlorhexidine 0.2%, was more effective as a preventive measure for VAP and in reducing oropharyngeal colonization. A Cochrane systematic review and meta-analysis reported that more evidence was needed regarding the use of chlorhexidine and its relation with reducing infection, mortality, and length of stay in the ICU.[274] Also, results from observational studies and a meta-analysis of RCTs showed an association between the use of chlorhexidine and increased mortality risk.[239 276-278] The micro-aspiration of chlorhexidine may cause ARDS[273 279] and could explain this harmful association. The use of chlorhexidine was also reported to be associated with adverse effects such as damage to oral mucosa (ie, erosive oral lesions, ulcerations, white or yellow plaques, and bleeding mucosa)[280] and hypersensitivity effects.[281 282] Additionally, a reported decrease in susceptibility to chlorhexidine is concerning.[283]

Finally, as part of SDD, short term and prophylactic systemic antibiotic treatment may be effective alone in patients who are urgently intubated after cardiac arrest or neurological injury. The use of 24-48 hour systemic antibiotic treatment may eradicate organisms that are aspirated during the intubation process and prevent the onset of VAP in the ensuing 48 hours.[284 285]

Emerging approaches to management

Investigations in metagenomics based on next generation sequencing (NGS) may significantly improve the diagnosis and treatment of pneumonia, especially in severe cases.[286-288] NGS allow for more accurate and rapid detection of multiple pathogens in a single assay. Plasma microRNA signatures have also emerged as a tool capable of predicting disease severity, being recently reported as a good marker of severity and deterioration of ICU patients with a diagnosis of covid-19.[289] Indeed, this technology may help clinicians provide more personalized management[290] in severe cases of pneumonia. Furthermore, evidence is growing for the value of technology, such as the Filmarray pneumonia test. This is a multiplex PCR assay that can detect the most commonly identified pathogens in pneumonia and their resistance patterns. Data on pathogen resistance have been recently published in a sub-study of the PROGRESS trial (a prospective and multicenter randomized trial).[291] The study included 56 patients with CAP and no risk factors for MDR pathogens, as well as another 34 patients with risk factors for MDR pathogens. Specifically, the pneumonia assay had a detection rate of 72%, whereas conventional microbiological testing had a rate of 10% (P<0.001). These results underpin the value of this new diagnostic test and its potential implementation in clinical practice in the future.

Guidelines

In formulating this review, we considered guidelines on the management of CAP, HAP, and VAP from the Infectious Diseases Society of America and the American Thoracic Society,[5 6] the European Respiratory Society, European Society of Intensive Care Medicine, European Society of Clinical Microbiology and Infectious Diseases, and Asociacion Latinoamericana del Torax.[5-7 12] Key recommendations are summarized above, and include likely pathogens, recommended diagnostic testing, choice of initial antimicrobial treatment, duration of treatment, use of adjunctive therapy, and prevention of pneumonia.

In patients with severe CAP, initial treatment is with the combination of a macrolide or fluoroquinolone, with a β-lactam. The β-lactam is chosen based on the presence of pseudomonal risk factors, and additional coverage for MRSA is also decided based on the presence of specific risk factors. Patients with documented influenza should receive oseltamivir,

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Questions for future research

- What is the value of molecular diagnostic testing in the definitive microbial diagnosis of severe pneumonia? What is its role in de-escalating antimicrobial treatment?
- How do we identify severe cases of pneumonia, early in the course of illness?
- How do we complement the combination of biomarkers and severity scores with clinical judgment to improve the identification of severe pneumonia?
- What are the characteristics of patients with severe CAP who might benefit from corticosteroids or other anti-inflammatory therapies?
- Can new antimicrobial agents help us more effectively manage patients who are infected with MDR pathogens?
- Is short course antibiotic treatment necessary in patients with severe viral pneumonia?

with the addition of antibiotics. Treatment is for a minimum of 5-7 days and duration may be guided by biomarkers such as procalcitonin. Adjunctive therapy with corticosteroids is not routinely recommended, but may have benefit for selected patients. Prevention is focused on vaccination of at-risk populations.

HAP/VAP remains a diagnostic challenge, and existing guidelines differ on the value of bronchoscopic samples, cultured quantitatively. Recommendations for therapy are to treat all patients for *P aeruginosa* and other Gram negatives pathogens, with coverage for MDR pathogens and MRSA, based on individual risk factors and the frequency of these pathogens in a given ICU. Newer agents and inhaled antibiotics may have a role for some highly resistant pathogens. Most patients will need combination treatment, and duration of therapy can be as short as seven days if initial therapy is accurate, the pathogen is not highly resistant, and the patient has responded well to therapy. Prevention is focused on available interventions such as head-of-bed elevation, prevention of aspiration, and a focus on decreased duration or avoidance of mechanical ventilation, early mobilization, and endotracheal tube cuff design.

Conclusions

Despite advances in diagnosis, management, antimicrobial therapy, and prevention, pneumonia continues to have a major impact on healthcare systems worldwide. The emergence of multidrug resistant pathogens, the increasing age of the population, the increased number of patients with multiple comorbidities and polypharmacy are some of the challenges that clinicians face in the management of critically ill patients with pneumonia. Despite some differences in the international guidelines for the management of CAP and HAP/VAP, following these recommendations will ensure better outcomes for patients admitted to the ICU with pneumonia.

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